ABSTRACT

Hypoxia-acidosis-associated cell death is mediated by BNIP3, a member of the Bcl-2 family of apoptosis-regulating proteins. Chronic hypoxia induced the expression and accumulation of BNIP3 mRNA and protein in cardiac myocytes but acidosis was required to activate the death pathway. Acidosis stabilized BNIP3 protein and increased the association with mitochondria. Cell death by hypoxia-acidosis was blocked by pretreatment with antisense BNIP3 oligonucleotides. The pathway included extensive DNA fragmentation and opening of the mitochondrial permeability transition pore but no apparent caspase activation. Overexpression of wild type BNIP3, but not a translocation-defective mutant activated cardiac myocyte death when the myocytes were acidotic or hypoxic.